REMARKS

Claims 1-148 were pending in the application. Claims 1-104 and 110-148 were withdrawn from consideration as directed to non-elected inventions. Claims 105-109 have been amended.

Claim 105 was amended to incorporate the limitations of claims 75 and 104, to remove reference to non-elected sequences, to indicate that the nucleic acid encodes a serotonin receptor, and to recite a specific level of homology. Claims 106-109 were amended to remove reference to non-elected sequences and to recite a specific level of homology. Claims 107 and 108 were amended to further clarify the claimed invention. Support for the claim amendments can be found throughout the specification as filed including, *inter alia*, in paragraph [00315], which indicates that the receptors are 5-HT_3 receptors.

The title has been amended as requested by the Office.

No new matter has been added.

Upon entry of this amendment, claims 105-109 will be pending.

Specification

The Office alleges that the title is not descriptive. Applicants respectfully disagree. However, in order to further prosecution, Applicants have amended the title.

In view of the foregoing, Applicants respectfully request that the objections to the specification be withdrawn.

Objections

Claims 105-109 stand objected for depending from non-elected claims or for reciting non-elected SEQ ID NOS. Claim 105 was amended to incorporate the limitations of claims 75 and 104. Claims 105-109 have been amended to update their dependencies and to remove reference to non-elected sequences.

In view of the foregoing, Applicants respectfully request that the objections to the claims be withdrawn.

Rejection under 35 U.S.C. §101

Claims 105-109 stand rejected under 35 U.S.C. § 101 because the claimed invention allegedly "is not supported by a specific, substantial and credible utility or a well- established utility." (Office Action, page 2). Applicants respectfully disagree.

The Office alleges that the "instant application has provided a description of an isolated protein. However, the instant application does not disclose a specific and substantial biological role of this protein or its significance." (Office Action, page 3). Applicants disagree.

The specification recites that the claimed receptor is a serotonin receptor and is useful, *inter alia*, in the treatment of anxiety, depression, pain, and dementia. Therefore, specific, substantial and credible utilities exist for the claimed receptors.

Utility Examination Guidelines

The Utility Examination Guidelines (the "Guidelines") require that a claimed invention have a specific, substantial and credible asserted utility, or, alternatively a well-established utility. Applicants have asserted that the claimed polypeptides are useful, *inter* alia, to generate antibodies specific for the claimed polypeptides. As discussed in greater detail below, the claimed polypeptides share 99% sequence homology with a known serotonin receptor. The fact that the claimed polypeptides share 100% sequence homology with a receptor with known function supports the assignment of the same specific, substantial, and credible utilities of serotonin receptors to the claimed polypeptides. The utilities asserted are art-established: those skilled in the art would readily acknowledge that the claimed polypeptides are useful within the meaning of 35 U.S.C. § 101.

Under the Guidelines, Office personnel are instructed to review the specification and claims of the application to determine if a specific and substantial utility that is credible is present. The Guidelines note that the specific and substantial requirement "excludes 'throw-away', insubstantial,' or 'nonspecific' utilities, such as the use of a

complex invention as landfill." The Guidelines go on to note that an Examiner's "*prima facie* showing ***must*** establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial." "If the applicant has asserted that the claimed invention is useful for any particular practical purpose (*i.e.*, it has a 'specific and substantial utility') and the assertion would be considered credible by a person of ordinary skill in the art, do ***not*** impose a rejection based on lack of utility." (Guidelines, emphasis added).

The Guidelines comment on the use of computer based analysis of nucleic acids to assign functions to a nucleic acid or polypeptide based upon homology to sequences found in databases. Specifically, the Guidelines state that the:

> suggestions to adopt a *per se* rule rejecting homology based assertions of utility ***are not adopted***. An applicant is entitled to a patent to the subject matter claimed unless statutory requirements are not met (35 U.S.C. 101, 102, 103, 112) . . .The inquiries involved in assessing utility are fact dependent, and the determinations must be made on the basis of scientific evidence. Reliance on the commenters' *per se* rule, rather than a fact dependent inquiry, is impermissible because the commenters provide no scientific evidence that homology-based assertions of utility are inherently unbelievable or involve implausible scientific principles. *See, e.g., In re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (rejection of claims improper where claims did 'not suggest an inherently unbelievable undertaking or involve implausible scientific principles' and where ''prior art * * * discloses structurally similar compounds to those claimed by the applicants which have been proven * * * to be effective').
>
> A patent examiner ***must*** accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. The examiner's decision must be supported by a preponderance of all the evidence of record. *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443,1444 (Fed. Cir. 1992). More specifically, when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. ''[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient.'' *Fujikawa* v. *Wattanasin,* 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996). The Office will take into account both the nature and degree of the homology.

> When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein. If the preponderance of the evidence of record, or of sound scientific reasoning, casts doubt upon such an asserted utility, the examiner should reject the claim for lack of utility under 35 U.S.C. 101. For example, where a class of proteins is defined by common structural features, but evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific, substantial, and credible utility to a new member of the class. When there is a reason to doubt the functional protein assignment, the utility examination may turn to whether or not the asserted protein encoded by a claimed nucleic acid has a well-established use. If there is a well-established utility for the protein and the claimed nucleic acid, the claim would meet the requirements for utility under 35 U.S.C. 101. If not, the burden shifts to the applicant to provide evidence supporting a well-established utility. There is no *per se* rule regarding homology, and each application must be judged on its own merits.

(Guidelines; emphasis added).

Preliminarily, Applicants remind the Office that specific and substantial utilities have been provided for the claimed polypeptides and that the asserted utilities are credible to one of skill in the art. The Office has failed to provide any evidence that "it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial."

Art-Recognized Utility

The Utility requirement may also be satisfied by an "Art Established Utility" which means that "a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention... and the utility is specific, substantial and credible." (M.P.E.P. §2107).

The claimed polypeptides are identified in the present application as 5-HT_3 receptors (*see* paragraph [00315]). Applicants respectfully point out that paragraphs [00211], [00212], [00240], among others of the present application, recite that the present

invention is useful, *inter alia*, as a diagnostic tool for diseases or disorders, wherein the disease is migraine, the pain associated with migraine, anxiety, depression, pain, and dementia.

Based on a BLAST alignment, SEQ ID NO:116 exhibited 99% sequence identity with known 5-HT_3 receptors (see attached alignment and reference cited therein). The probability, therefore, that the claimed polypeptides' function and structure are related to those of the 5-HT_3 receptor is, accordingly, extremely high. The Office has failed to provide any "countervailing evidence" required by the Utility Examination Guidelines to show that the relationship does not exist. Therefore, no countervailing evidence that says the present invention does not have a substantial, credible, and useful invention has been provided.

Ion channel proteins in general have a well-established utility. Many medically significant biological processes mediated by signal transduction pathways involving ion channels are recognized as important therapeutic targets for a wide range of diseases. In this respect, the ion channel family is analogous to the chemical genus that was the subject of *In re Folkers*, 145 USPQ 390 (CCPA 1965) (Compound that belongs to class of compounds, members of which are recognized as useful, is considered useful under §101.) The Patent Office does not serve the public by attempting to substitute a formulaic analysis of § 101 for the established judgment of the biopharmaceutical industry as to what is "useful." If the Patent Office is aware of any well-grounded scientific literature suggesting that ion channels are not useful, Applicants request that it be made of record.

Moreover, the utility of serotonin receptors is well-established. Serotonin receptors are known to play roles in many human diseases and disorders. As discussed in the attached review article (Glennon et al.), 5-HT_3 receptors "can control dopamine release and may also be involved in acetylcholine relases and control of the GABAergic system." The article further notes that 5-HT_3 antagonists "have proven clinically effective for the treatment of chemotherapy-induced or radiation-induced nausea and vomiting . . . [and] may be effective in the treatment of migraine of the pain associated

with migraine. Preclinical studies suggest that 5-HT_3 antagonists may enhance memory and be of benefit in the treatment of anxiety, depression, pain, and dementia."

Glennon et al. further supports the assignment of the well-known utilities of receptors in the 5-HT_3 family to the presently claimed polypeptides. Glennon notes that:

> "[a]ny two receptors whose amino acid sequences are about 70–80% identical in their membrane-spanning segments may have highly similar to nearly indistinguishable pharmacological profiles and/or second messenger systems. Such closely related receptors (i.e., an intermediate-homology group) can be considered members of the same subfamily. In addition, there is a low-homology group (35–55% TM homology) that consists of distantly related receptor subtypes from the same neurotransmitter family, and there is also a high-homology group (95–99% TM homology) that consists of species homologs from the same gene in different species.

(Glennon et al.) Applicants respectfully assert that the presently claimed polypeptides, as set forth in the attached alignment, are in the same "high-homology group" as known serotonin receptors, and are therefore "species homologs from the same gene." Id.

Applicants note for the record that the Patent Office has issued patents in the field of ion channels for applications disclosing the same amount of information as is described in the present application. The Office has granted and apparently continues to grant patents to ion channel proteins, their encoding polynucleotides and antibodies directed to them ***in which no specific biological activity has been confirmed.*** Specifically, Applicants would like to bring the following US Patents to the Office's attention:

6,562,593 Merkulov *et al.* "Isolated human transporter proteins, nucleic acid molecules encoding human transporter proteins, and uses thereof" (Claims an isolated polynucleotide and method for producing polypeptide)
6,503,733 Bandman *et al.* "Human anion channel" (Claims an isolated polynucleotide, an isolated polypeptide and an antibody that binds to the polypeptide)
6,228,616 Bandman *et al.* "Human anion channel" (Claims a purified antibody)
5,854,411 Goli *et al.* "Human Chloride Channel" (Claims an isolated polynucleotide)
6,451,554 Wood *et al.* "Ion Channel" (Claims an isolated polynucleotide and a method of producing a polypeptide encoded by the polynucleotide.)
6,309,858 Dietrich *et al.* "T-type calcium channel variants; compositions thereof; and uses" (Claims an isolated polynucleotide).

6,309,855 Duprat *et al.* "Family of mammalian potassium channels, their cloning and their use, especially for the screening of drugs" (Claims isolated polynucleotide)
6,207,410 Hall *et al.* "Genes encoding an insect calcium channel" (Claims isolated polynucleotide and methods)
6,087,488 Ganetzky *et al.* "Potassium ion channel genes and proteins" (Claims isolated polynucleotide)
6,013,474 Ellis *et al.* "Calcium channel compositions and methods" (Claims isolated polynucleotide)
5,710,019 Li *et al.* "Human potassium channel 1 and 2 proteins" (Claims an isolated polypeptide)

Applicants submit that these issued US Patents are evidence of an art recognized utility for ion channels whose natural function or association with disease is unproven. Upon review of the file histories of several of the above-identified patents, it is apparent that the present application provides at least as much functional data as the applications giving rise to the issued patents provided. For example, U.S. Patent 6,562,593 is directed to:

> An isolated nucleic acid molecule consisting of a nucleotide sequence selected from the group consisting of:
> (a) a nucleotide sequence that encodes a protein comprising the amino acid sequence of SEQ ID NO:2;
> (b) a nucleotide sequence consisting of the nucleic acid sequence of SEQ ID No:1; and
> (c) a nucleotide sequence that is completely complementary to a nucleotide sequence of (a)-(b).

(claim 1). The specification of the patent reveals that the claimed sequences were "related to the differentiation-associated Na-dependent inorganic phosphate cotransporter subfamily." (*see* column 11, lines 34-55) . Based on this disclosure it is assumed that the physiological role of the claimed channel is in the transport of inorganic phosphate. The specification further provides sequence information, and the putative identification of structural elements including start codon, stop codon, and phosphorylation sites (*see* Figure 1).

The present application provides analogous information to that set forth by U.S. Patent 6,562,593. For example, the application indicates that the claimed polypeptides are serotonin receptors. Sequence information relating to the claimed polypeptides is

included throughout the specification and the appended sequence listing. Also, the present application provides expression data relating to the claimed polypeptides.

A brief review of commercially available serotonin receptor products reveals several products specifically related to the 5-HT_3 receptor. For example, Imgenex sells a polyclonal antibody directed to the 5-HT_3 receptor (*see* attached product sheet). Also, several companies are marketing 5-HT_3 receptor antagonists including: *Kytril*® (anti-nausea drug; see Chugai Pharmaceutical Company's Annual Report, attached hereto); *Aloxi*™ (palonosetron) Helsinn Healthcare; for acute and delayed nausea and vomiting associated with chemotherapy; see Aloxi™ press release, attached hereto); *Anzemet*® (dolasetron mesylate; Hoechst Marion Roussel; for the prevention of nausea and vomiting in patients undergoing single or repeated courses of emetogenic cancer chemotherapy; see product sheet attached hereto); *Lotronex*® (alosetron; GlaxoWellcome; for the treatment of irritable bowel syndrome (IBS); see Mosby's Drug Consult™ 2000; copy attached hereto). The fact that companies make and sell such products proves that there is a well-established utility for the presently claimed polypeptides.

Accordingly there could be no better proof of the utilities of the claimed polypeptides- such products are made by a manufacturer (who expects to sell them) for consumers (who expect to buy them). Any argument that there is no art-recognized utility for such polypeptides seems meritless.

Specific Utility

The Utility Examination Guidelines require a claimed invention to have a utility that is specific to the subject matter claimed (a "specific utility"). As acknowledged by the Office, the presently claimed invention can be used for many different purposes. The present application recites, for example, that the claimed invention can be used, *inter alia*, to generate antibodies specific for the claimed polypeptides or as ion channels. Thus, there is no question that Applicants have asserted at least one specific utility and, in

fact, have provided numerous specific utilities for the polypeptides of the present invention.

Additionally, the Office appears to be under the assumption that ***absolute*** certainty is required for a polypeptide to have a specific utility. The Office states, "There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Applicant's' claimed invention is incomplete." (Office Action, page 3).

The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability as the Supreme Court stated applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner v. Manson*, 383 U.S. at 532. Although, there may be numerous inventions that may arise from the present application, this standard does not justify the Office's stance that the present invention lacks a specific utility. Thus, Applicants have complied with the specific utility requirement.

The Training Materials associated with the Utility Examination guidelines address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials further distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," or unique (Training Materials at p.52) as compared to the "broad class of invention." Applicants note that such "unique" or "particular" utilities never have been required by the law.

To meet the utility requirement, the invention must be "practically useful," *Anderson v Natta*, 480 F.2d 1392, 1397 (CCPA 1973) and confer a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534 (1966). The threshold of utility under this standard is not high, and requires merely an "identifiable" benefit. *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180 (Fed. Cir. 1991), the CAFC explained that "An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

This does not preclude, however, a general utility. Practical real-world uses are ***not*** limited to uses that are unique to a single invention. The law requires that the practical utility be "definite," not particular to only one invention. *Standard Oil Co. v. Montedison,* 664 F.2d 356, 375 (3d Cir. 1981). The courts have not rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention; where courts have found utility to be too "general," it has been in situations when the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

Inventions that achieve a practical use, a use that is also achieved by other inventions, satisfy the utility requirement. Thus practical utilities can be directed to classes of inventions, so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. *Montedison*, 664 F.2d at 374-75. For example, many materials conduct electricity. This general utility applies to a broad class of inventions (conductive materials) and satisfies the utility requirement of section 101. The fact that other materials also conduct electricity does ***not*** mean that

other materials that conduct electricity want for utility. What is important, however, is that ion channels are known to have practical uses. For example, ion channels all have practical uses well beyond throwaway uses like snake food. All of the genes encoding ion channels can be used, for example, for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular ion channel works. No additional experimentation would be required, therefore, to determine whether an ion channel has a practical use as all ion channels have at least one practical use.

The Office appears to be under the impression that inventions that are, *inter alia*, useful for use in research are unpatentable. This is not true. The Patent Office's patent database is replete with patents claiming useful research tools, *e.g.*, spectrophotometers. A material whose only use is as a tool in research may indeed be patentable. *Brenner* and *Kirk* exclude only those research purposes where the ***only*** use of the material itself is as the subject of research. If *Brenner* and *Kirk* had held otherwise, any chemical material would, by virtue of its existence, be useful. However, nowhere do those cases state or imply that a material cannot be patentable if has some other beneficial use in research.

Assay methods, like many other tools used in research, have an immediately realizable "real world" value. For example, an assay method that can identify chemical compounds that possess a particular physical, structural or biological property clearly have "real world" value irrespective and independent from the utility that may be associated with the compounds identified using the assay method. As a consequence, a presumption that assay methods cannot possess utility if the compound isolated or identified using the assay do not have utility would be the product of a flawed analysis of *Brenner*. Such a conclusion also would suggest that processes and products can never possess utility if their utility lies in the field of research. Indeed, the application of this concept of the utility requirement as it relates to methods for assaying or identifying compounds, if taken literally, would mean that claims to methods such as NMR, infrared, x-ray crystallography, and screening for other important biological properties, would be unpatentable because further research would be necessary to establish utility for the

compounds identified or assayed. This certainly cannot be the result intended by the Patent Office when issuing these guidelines.

Because all ion channels, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there should be no need to provide additional information about them. A person of ordinary skill in the art need not guess whether any given ion channel conveys a practical benefit. Nor is it necessary to know how or why any given ion channel works. It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581 (Fed. Cir. 1989).

Applicants need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532. The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326 (CCPA 1980). "The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs." *Id.* Unless there is proof of "total incapacity," or there is a "complete absence of data" to support the applicant's assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762. The Office has failed to provide proof of "total incapacity", and Applicants have provided information that supports the asserted utilities.

The Office is also reminded that a patent applicant's assertion of utility in the disclosure is presumed to be true and correct. *In re Cortwright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Id.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the

applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566.

As discussed, the claimed polypeptides are closely related to the serotonin family of receptors. Applicants have demonstrated a "substantial likelihood" of utility by showing a "reasonable correlation" between the utility of the known composition (serotonin receptors, in particular 5-HT_3 receptors) and the composition being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565 (Fed. Cir. 1996). The Office has neither provided evidence nor sound scientific reasoning that one skilled in the art would doubt the "reasonable correlation" advanced by Applicants. Accordingly, under *Brana*, the Patent Office ***must*** accept the utility asserted by Applicants.

Substantial Utility

In addition to conferring a specific benefit on the public, the benefit must also be "substantial". *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA 1980). An asserted utility for a compound that merely invites further research to determine a practical utility is not substantial. In *Brenner*, for example, the U.S. Supreme Court held that a process for making a compound does not confer substantial benefit where the only known use of the compound was to be the object of further research. *Id.* at 535. Similarly, in *In re Kirk*, the CCPA held that compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 945.

Applicants teach, as described above, that the claimed invention can be used for the production of antibodies and as a serotonin receptor, and is useful for the treatment and/or diagnosis of anxiety, depression, pain, and dementia. Thus, it is clear that the claimed invention has real-world uses. All the uses described in the present application are real-world uses and, again, stand in stark contrast to the "throw away" uses (*e.g.*, landfill component or snake food) set forth in the utility guidelines. Thus, there is no question that Applicants have asserted at least one substantial utility and, in fact, have

provided numerous substantial utilities. Accordingly, Applicants have complied with the substantial utility requirement.

The Office appears to be under the impression that inventions that are, *inter alia*, useful for use in research are unpatentable. This is not true. The Patent Office's patent database is replete with patents claiming useful research tools, *e.g.*, spectrophotometers. A material whose only use is as a tool in research may indeed be patentable. *Brenner* and *Kirk* exclude only those research purposes where the ***only*** use of the material itself is as the subject of research. If *Brenner* and *Kirk* had held otherwise, any chemical material would, by virtue of its existence, be useful. However, nowhere do those cases state or imply that a material cannot be patentable if has some other beneficial use in research.

Assay methods, like many other tools used in research, have an immediately realizable "real world" value. For example, an assay method that can identify chemical compounds that possess a particular physical, structural or biological property clearly have "real world" value irrespective and independent from the utility that may be associated with the compounds identified using the assay method. As a consequence, a presumption that assay methods cannot possess utility if the compound isolated or identified using the assay do not have utility would be the product of a flawed analysis of *Brenner*. Such a conclusion also would suggest that processes and products can never possess utility if their utility lies in the field of research. Indeed, the application of this concept of the utility requirement as it relates to methods for assaying or identifying compounds, if taken literally, would mean that claims to methods such as NMR, infrared, x-ray crystallography, and screening for other important biological properties, would be unpatentable because further research would be necessary to establish utility for the compounds identified or assayed. This certainly cannot be the result intended by the Patent Office when issuing these guidelines.

The claimed invention in *Brenner* was directed to a method whose ***only*** utility was making a class of steroids. The disclosure in Brenner failed to disclose a utility for the products of that method, which in turn led to a § 101 rejection because the products resulting from the method lacked utility. The Applicant admitted that the products

produced by the method would not be patentable if they lacked utility. 148 USPQ 696. The Court stated that the method lacked utility as well, holding:

> We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product.

148 USPQ 696.

In *Brenner*, the method of making the compounds, which was the only use recited, was inextricably bound up with the compounds themselves and, as a result, the requirement for utility could not be met until a use for the compounds was found. The Court emphasized that the utility of the claimed invention (i.e., the products) would require further research to identify and ascertain, and the compounds produced by the method would be the objects of that research.

In contrast, ion channels related to known ion channels stand on a very different basis. As discussed, there are a multitude of utilities for the claimed polypeptides, including, but not limited to, their ability to facilitate research.

The Claimed Invention Has A Credible Utility

In addition to a specific and substantial utility, the Utility Examination Guidelines require that such utility be "credible" (a "credible utility"). That is, whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. Clearly, the numerous specific and substantial utilities asserted by Applicants are credible. Assertions of credibility are credible unless "(A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion." (See, Revised Interim Utility Guidelines Training Materials). Further, the PTO is reminded that it must treat as true a statement of fact made by Applicants in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. All the utilities described for the polypeptides of the present invention are based on sound logic.

The Office has provided no evidence that the logic is seriously flawed or that the facts upon which these assertions are based are inconsistent with the logic underlying the assertions.

The Office has failed to provide any "countervailing evidence" required by the Utility Examination Guidelines to show that the relationship does not exist. Therefore, no countervailing evidence that says the present invention does not have a substantial, credible, and useful invention has been provided.

Applicants further assert that long held pre-Brenner case law standard supports judging the utility of an invention on whether or not the public derives a benefit from the invention, regardless of how slight the benefit. *See,* for example, *In re Nelson*, 280 F.2d 172, 178-180 (C.C.P.A. 1960) (stating that "however slight the advantage which the public have received from the inventor, it offers a sufficient reason for his compensation") (citing ROBINSON ON PATENTS (1890)); *see also Lowell v. Lewis*, 1 Mason 182 (Fed. Case. No. 8568, 1817) (stating "if it be more or less useful is... of no importance to the public. If it be not extensively useful it will silently sink into contempt and disregard"). Polypeptides of all types are broadly used in the biotechnology industry, playing key roles in drug and disease discovery processes. Indeed, many such fragments enable researchers to find the genes associated with physiological functions. The discovery of such functions readily benefits the public. Accordingly, such tools should satisfy the pre-Brenner case law standard.

Applicants have demonstrated a "substantial likelihood" of utility by showing a "reasonable correlation" between the utility of the known compositions (trace amine receptors) and the composition being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565 (Fed. Cir. 1996). The Office has neither provided evidence nor sound scientific reasoning that one skilled in the art would doubt the "reasonable correlation" advanced by Applicants. Accordingly, under *Brana*, the Patent Office ***must*** accept the utility asserted by Applicants.

References Cited by the Office

The Office cites references that are said to provide evidence that "function cannot be predicted based solely on structural similarity to a protein found in the sequence databases." (Office Action, page 3). Applicants respectfully disagree with the Office's characterization of the cited references.

None of the cited references, however, state that functional homology cannot be inferred by a reasonable probability in any particular case. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over many amino acid residues is exceedingly small. Brenner *et al.*, *Proc. Natl. Acad. Sci.* **95**:6073-78 (1998) (See, attached reference). The Examiner is reminded that the presently claimed polypeptides share well over 40% sequence homology over almost 500 amino acids with known serotonin receptors, indeed, as set forth above, the claimed polypeptides share 99% sequence homology with receptors in the 5-HT_3 family.

Scolnick *et al.* (Trends in Biotech., 18:34-39, 2000), for example, does not say that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Instead, Scolnick states that "the sequence-to-function approach is the most commonly used function-prediction method. This robust filed is well developed . . .". Although Scolnick acknowledges that there are limitations to sequence-based approaches, Scolnick indicates that "for proteins whose sequence identity is above ~30%, one can use homology modeling . . .". Applicants remind the Office that in the present application, homology with a known serotonin receptor is 99%. Further, Scolnick states that even if inexact models (of protein structure) are used, based on homology, "structure from sequence can be used for the subsequent prediction of biochemical function." (Scolnick, page 35).

Bork *et al.* (Trends in Genetics, 12:425-427, 1996) points out problems in the use of sequence databases. Interestingly, Bork notes that even as early as 1996 (the publication date of the reference) the accuracy of gene identification was between 60-

70%. In contrast, in Bork's later reference, discussed below, according to Table 1, the accuracy of predicting "functional features by homology" is said to be 90%.

Bork (Genome Research 10:398-400, 2000) discusses "Powers and Pitfalls in Sequence Analysis." Although Bork notes that computational sequence analysis is "far from being perfect", Bork states that the percent accuracy in determining functional features based on homology is 90%. (See Table 1).

Similarly, Doerks *et al.* (Trends in Genetics, 14:248-250, 1998) does not say that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Doerks discusses faulty characterization of UPFs (uncharacterized protein families). By definition UPFs contain members in at least 3 taxonomically and phylogenetically distinct species and do not contain biochemically-characterized proteins. Using, *inter alia*, sequence homology, Doerks was able to provide functional annotation for "more than 700 of the 1300 proteins clustered in 25 of the 58 distinct UPFs. . . . , for another 13 UPFs currently containing about 250 proteins, the presence of transmembrane regions was recorded. *Id.*" (Doerks, page 250). Although Doerks acknowledges that there are pitfalls to be avoided in annotating protein sequences, the fact that Doerks was able to ascribe a function to more than 700 out of 1300 proteins and to identify structural elements in another 250 proteins indicates that function can be predicted based on sequence similarity.

Smith *et al.* (Nature Biotechnology, 15:1222-1223, 1997) does not say that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Instead, Smith states that "the major problems associated with nearly all the current automated annotation approaches are- paradoxically – minor database annotation inconsistencies (and a few outright errors)." (Smith, page 1222).

Brenner (Trends in Genetics, 15:132-133, 1999) discusses "Errors in genome annotation". Although Brenner alleges that there are problems with inferring function from homology, the data presented does not support the Office's position that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Instead Brenner supports the use of sequence-function prediction.

Indeed, on reviewing Table 1 on page 133, it appears that the highest "minimum error rate" in annotating genes was calculated to be 15%. If this is to be believed, it must be assumed then that at most, 85% of the annotations were correct.

As discussed above, under *Brenner* Applicants need only prove a "substantial likelihood" of utility. Certainly, the references cited by the examiner do not state that functional homology cannot be inferred by a reasonable probability. Indeed, most of the cited cases indicate that function can reasonably be inferred based on homology.

Summary of 35 U.S.C. § 101 Issues

The Utility Examination Guidelines note that an Examiner's "*prima facie* showing ***must*** establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial." "If the applicant has asserted that the claimed invention is useful for any particular practical purpose (*i.e.*, it has a 'specific and substantial utility') and the assertion would be considered credible by a person of ordinary skill in the art, do ***not*** impose a rejection based on lack of utility." Applicants have asserted that the claimed polypeptides are useful, *inter* alia, to generate antibodies specific for the claimed GPCR polypeptides. As discussed the claimed polypeptides share 99% sequence homology with known serotonin receptors, receptors known to be involved in anxiety, depression, pain, and dementia, *inter alia*. The fact that the claimed polypeptides share such sequence homology with known receptors supports the assignment of the same specific, substantial, and credible utilities of serotonin receptors to the claimed polypeptides. The utilities asserted are by Applicants art-established: those skilled in the art would readily acknowledge that the claimed polypeptides are useful within the meaning of 35 U.S.C. § 101.

A patent examiner ***must*** accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. The Guidelines make clear that when a patent application claiming a nucleic acid, for example, asserts a specific, substantial, and credibility, and bases the assertion upon homology to existing

nucleic acids or proteins having an accepted utility, the asserted utility ***must*** be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. The Office has failed to provide any evidence, less still a preponderance of the evidence, to cast doubt upon any of the asserted utilities. The Office has also failed to provide any evidence that the asserted utilities are "throwaway utilities" or that the claimed polypeptides are inappropriate or unsuited for the several asserted utilities. Finally, even assuming *arguendo* that the asserted utilities are not specific or substantial, the art established utilities for the claimed polypeptides satisfy the Utility requirement of § 101.

Applicants therefore respectfully request the withdrawal of the rejection under 35 U.S.C. § 101.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 105-109 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to adequately teach how to use the instant invention. According to the Office, "since the claimed invention is not supported by a specific, substantial, and credible asserted utility or a well established utility...one skilled in the art clearly would not know how to used the claimed invention." (Office Action, page 5) Applicants respectfully disagree.

As discussed above, the present invention ***is*** supported by a specific, substantial, and credible asserted utility as well as a well-established utility. Applicants respectfully request that the rejection be withdrawn.

Although acknowledging that the specification is "enabling for SEQ ID NO:116" the Office alleges that the specification "does not reasonably provide enablement for polypeptides which are 'homologous' to any proteins, including those having 'at least one conservative amino acid substitution,' or for nucleic acids encoding 'at least a portion' of ion-x." (Office Action, page 5).

Although Applicants respectfully assert that the art-skilled could without any undue burden make and use the claimed invention upon reading the present specification,

Applicants have amended claims 105-109. As amended, the claims no longer recite the terms "at least one conservative amino acid substitution" or for nucleic acids encoding "at least a portion' of ion-x." The claims have also been amended to recite specific levels of homology.

Claim 108 was rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention allegedly "is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Office alleges that the term "allelic variants" is undefined in the specification and that the term "does not have any particular connotation as to the encoded protein." (Office Action, page 6). Applicants do not agree.

Although Applicants assert that the art-skilled would readily the pending claims and would be able to make and use the claimed invention, solely in an attempt to advance the prosecution of the present invention, Applicants have amended the claims. As amended, the claims no longer recite the term "allelic variant."

Claims 105-109 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention."[1] The Office alleges that "[p]olynucleotides which comprise 'at least a portion' of ion-x would have one or more nucleic acid substitutions, deletions, insertions and/or additions to said polynucleotide. Similarly, polypeptides which are 'homologous' to, or have 'at least one conservative amino acid substitution' to SEQ ID NO 116 would encode for a protein with one or more amino acid substitutions, deletions, insertions and/or additions to the protein encoded for by SEQ ID NO:116." The Office notes that the "specification and claims do not indicate

[1] Applicants note that the Office rejects claim 8 under 35 U.S.C. § 112, first paragraph, on page 8 of the Office Action. Applicants assume this is a typographical error as claim 8 was withdrawn from

what distinguishing attributes are shared by the members of the genus." (Office Action, page 7). Applicants disagree.

Notwithstanding the foregoing, Applicants have amended claims 105-109 to recite specific levels of homology. The claims no longer recite "at least a portion of".

The PTO has promulgated guidelines for the application of the written description requirement in the "Revised Interim Written Description Guidelines Training Materials" (hereinafter "Written Description Guidelines"). Applicants respectfully direct the Examiner's attention to the Examples set forth therein, one of which is reproduced below:

> **Example 14: Product by Function**
> **Specification:** The specification exemplifies a protein isolated from liver that catalyzes the reaction of A→B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.
> **Claim:**
> A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A→B.
> **Analysis:**
> A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.
> A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which

consideration and is drawn to an expression vector. Applicants note, however, that the comments set forth herein respond to the Examiner's assertions regarding written description support for the pending claims.

comprises SEQ ID NO:3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".

The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.

There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.

Applicants respectfully assert that the claimed invention complies with the written description requirement of 35 U.S.C. §112, first paragraph. The claims, as amended, are analogous to the exemplary claim recited in Example 14 of the Written Description Guidelines set forth above, minus the requirement in the exemplary claim of a catalytic activity. In the exemplary claim, homologs having 90%/95%/99% sequence homology to SEQ ID NO:116 are recited. The analysis set forth in the Guidelines states that "the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must . . . have at least 95% identity to the reference sequence, SEQ ID NO: 3. . ." and that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for

identifying all of the at least 95% identical variants of SEQ ID NO: 3 . . .". The Written Description Guidelines further state that "[o]ne of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus" and that "the disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention."

Applicants respectfully assert that the genera of proteins claimed comply with the written description requirement. The genera encompassed by claims 105-109 do not have substantial variation since all species within the genera must encode a serotonin receptor. Applicants provide a stated degree of homology which imposes a further structural relationship between members of the genera.

Applicants also provide methods for assaying for ion channel polypeptide-interacting proteins (Example 7), methods for analyzing protein-protein interactions involving ion channel polypeptides (Example 8), and assays to identify modulators of ion channel activity (Example 9).

Applicants are ***not*** required to provide a specification that describes anything and everything upon which the claims could ever be construed to read. If Applicants were held to such a standard, no specification could ever be deemed to meet the written description requirement. As previously discussed, the specification adequately describes ***the subject matter defined by the present claims***, which is all that the law requires.

The Office Action has failed to provide any evidence or reasoning why the specific species described, along with a description of the attributes and features of the polypeptides that comprise the claimed genera, does not constitute adequate description of the claimed subject matter. One of skill in the art would conclude that Applicants were in possession of the necessary common attributes possessed by the members of the genera and that the disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.

Vas-Cath and *University of California* were cited to support the Office's assertion that the pending claims did not satisfy the Written Description requirement. Applicants respectfully assert that persons of ordinary skill in the art would recognize that

Applicants invented what is claimed. As discussed above, the pending claims provide Written Description support for themselves as they are virtually identical to those originally filed. Applicants remind the Examiner that additional Written Description support is found throughout the application as originally filed and, thus, the citation of *Vas-Cath* does nothing to support the Examiner's position.

University of California v. Eli Lilly and Co. are distinguishable from the present facts. The Written Description Guidelines discuss the *University of California* scenario in Example 7 and state that the exemplary claim (An isolated DNA comprising SEQ ID NO: 16) does not satisfy the written description requirement because "[t]he present claim encompasses full-length genes and cDNAs that are not further described. There is substantial variability among the species of DNAs encompassed within the scope of the claims because SEQ ID NO:16 is only a fragment of any full-length gene or cDNA species. When reviewing a claim that encompasses a widely varying genus, the examiner must evaluate any necessary common attributes or features."

Again, as discussed in greater detail above, the pending claims do satisfy the written description guidelines because, *inter alia*, there is no "substantial variation among the species of polypeptides" – a minimum of 95% sequence homology is required to SEQ ID NO:116, and a functional limitation is set forth. Applicants respectfully point out that the facts relating to the pending claims are analogous to Example 14 of the "The Revised Interim Written Description Guidelines Training Materials", in which the exemplary claim is said to satisfy the Written Description Requirement.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 105-109 were rejected under 35 U.S.C. § 112, second paragraph. The Office alleges that the terms "ion-x" and "a portion of" render the claims indefinite. Applicants do not agree.

Although one of skill in the art would readily understand the metes and bounds of the terms "ion-x" and "a portion of", claims 105-109 have been amended. As amended,

the claims no longer recite "ion-x" and "a portion of", thus rendering the current rejection moot.

Rejection under 35 U.S.C. § 102

Claims 106 and 107 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Dubin *et al.* The Office alleges that "Dubin *et al.* teach a protein which is 71.7% identical to SEQ ID NO:116 [and that] [t]his protein meets the limitation of 'homologous' especially in the absence of any limitations of definition of the term 'homologous'." (Office Action, page 10). Applicants respectfully traverse the rejection because Dubin *et al.* fails to teach or suggest all the elements of the present invention.

Claims 106 and 107, as amended, recite a polypeptide with at least 98/99% sequence homology to SEQ ID NO:116. Dubin *et al.* fails to teach a polypeptide with at least 98/99% sequence homology to SEQ ID NO:116. Because Dubin et al fails to teach or suggest every element of the invention, the claims are not anticipated. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 102(b).

Claims 106 and 107 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Wood *et al.* (WO01/68849; cited on the IDS submitted January 30, 2003, as reference "AC"). The Office alleges that Wood *et al.* recites "a protein which is 97.8% identical to SEQ ID NO:116 [and that] [t]his protein meets the limitation of 'homologous' especially in the absence of any limitations of definition of the term 'homologous'." (Office Action, page 11). Applicants respectfully disagree.

To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.*, 334 U.S.P.Q.2d 1565 (Fed. Cir. 1995).

Claims 106 and 107, as amended, recites a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence, said nucleotide sequence having at least 95% sequence homology

to a sequence of SEQ ID NO:115, wherein said nucleic acid molecule encodes a serotonin receptor, wherein said polypeptide comprises a an amino acid sequence with at least 98%[99%] sequence homology to a sequence of SEQ ID NO:116. Wood fails to disclose every feature of the pending claims, as amended, in particular wherein the nucleotide sequence encoding the polypeptide has "at least 95% sequence homology to a sequence of SEQ ID NO:115." Because Wood fails to teach or suggest every element of the invention, the claims are not anticipated. Accordingly, Applicants respectfully requests reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 102(e).

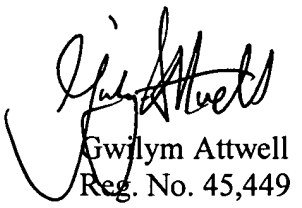
Common Ownership

Applicants note that the Wood *et al.* patent publication and the present application are commonly assigned to Pharmacia & Upjohn Co. The present application was filed after November 29, 1999. Accordingly, the Wood *et al.* patent publication would be disqualified as prior art against the present invention under 35 U.S.C. § 102(e)/103 or 103.

Conclusion

Applicants believe the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-6904 to clarify any unresolved issues raised by this response.

Respectfully submitted,



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Attachments: Brenner *et al.* (Proc. Natl. Acad. Sci. **95**:6073-78, 1998)
Glennon *et al.* (Neuropsychopharmacology: The Fourth Generation of Progress, 2000)
Imgenex Product Sheet
Sequence Alignment and NCBI reference locator
Chugai Annual Report
Aloxi™ press release
Anzemet® Product Sheet
Mosby's Drug Consult™ 2000